Applicant : Shigeaki Kato et al.   Attorney's Docket No. 06501-054001 / C1-901PCT-
Serial No. : 09/489,198   US
Filed : January 20, 2000
Page : 3

REMARKS

Applicants hereby submit that the enclosures fulfill the requirements under 37 C.F.R. §1.821-1.825. The amendments in the specification merely insert the paper copy of the Sequence Listing and sequence identifiers in the specification. In particular, the description of Figure 4 has been amended to insert a sequence identifier. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment.

Please apply any charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Aug. 31, 2001
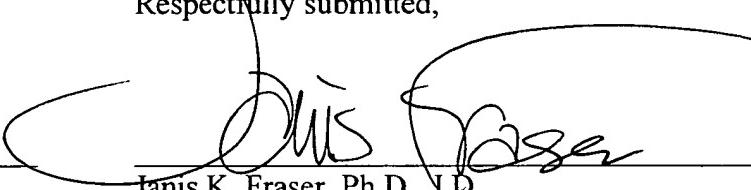
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, Massachusetts 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

20308039.doc

**"Version With Markings to Show Changes Made"**

<u>In the specification:</u>

Paragraph beginning at page 22, line 19, has been amended as follows:

Figure 4 shows the putative amino acid sequenec of CYP1AD <u>(SEQ ID NO:1)</u>. The first methionine is assigned as position 1. Asterisk indicates the terminal codon. Putative mitochondria targeting signal is surrounded by square. Underline indicates sterol binding domain. Dotted underline indicates hem-binding domain.
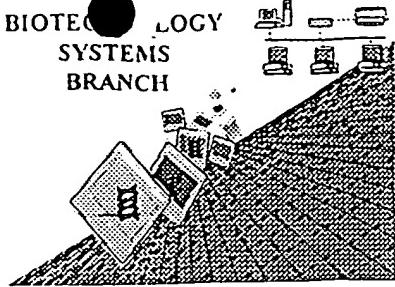
RAW SEQUENCE LISTING
ERROR REPORT

BIOTECHNOLOGY
SYSTEMS
BRANCH

The Biotechnology Systems Branch of the Scientific and Technical Information Center (STIC) detected errors when processing the following computer readable form:

Application Serial Number: _09/489,198_

Source: _1646_

Date Processed by STIC: _6-14-01_

THE ATTACHED PRINTOUT EXPLAINS DETECTED ERRORS.
PLEASE FORWARD THIS INFORMATION TO THE APPLICANT BY EITHER:
1) INCLUDING A COPY OF THIS PRINTOUT IN YOUR NEXT COMMUNICATION TO THE APPLICANT, WITH A NOTICE TO COMPLY or,
2) TELEPHONING APPLICANT AND FAXING A COPY OF THIS PRINTOUT, WITH A NOTICE TO COMPLY
FOR CRF SUBMISSION QUESTIONS, PLEASE CONTACT MARK SPENCER, 703-308-4212.

FOR SEQUENCE RULES INTERPRETATION, PLEASE CONTACT ROBERT WAX, 703-308-4216.
PATENTIN 2.1 e-mail help: patin21help@uspto.gov or phone 703-306-4119 (R. Wax)
PATENTIN 3.0 e-mail help: patin3help@uspto.gov or phone 703-306-4119 (R. Wax)

TO REDUCE ERRORED SEQUENCE LISTINGS, PLEASE USE THE CHECKER VERSION 3.0 PROGRAM, ACCESSIBLE THROUGH THE U.S. PATENT AND TRADEMARK OFFICE WEBSITE. SEE BELOW:

Checker Version 3.0

The Checker Version 3.0 application is a state-of-the-art Windows based software program employing a logical and intuitive user-interface to check whether a sequence listing is in compliance with format and content rules. Checker Version 3.0 works for sequence listings generated for the original version of 37 CFR §§1.821 – 1.825 effective October 1, 1990 (old rules) and the revised version (new rules) effective July 1, 1998 as well as World Intellectual Property Organization (WIPO) Standard ST.25.
Checker Version 3.0 replaces the previous DOS-based version of Checker, and is Y2K-compliant. Checker allows public users to check sequence listings in Computer Readable form (CRF) before submitting them to the United States Patent and Trademark Office (USPTO).
Use of Checker prior to filing the sequence listing is expected to result in fewer errored sequence listings, thus saving time and money.

Checker Version 3.0 can be down loaded from the USPTO website at the following address:
http://www.uspto.gov/web/offices/pac/checker
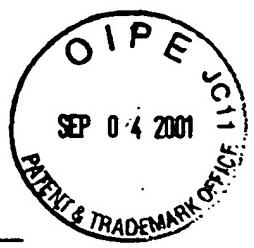
Raw Sequence Listing Error Summary

ERROR DETECTED   **SUGGESTED CORRECTION**   SERIAL NUMBER: _09/489, 198_

ATTN: NEW RULES CASES: PLEASE DISREGARD ENGLISH "ALPHA" HEADERS, WHICH WERE INSERTED BY PTO SOFTWARE

1 ____ Wrapped Nucleics   The number/text at the end of each line "wrapped" down to the next line. This may occur if your file
     Wrapped Aminos ·   was retrieved in a word processor after creating it. Please adjust your right margin to .3; this will
     prevent "wrapping."

2 ____ Invalid Line Length   The rules require that a line not exceed 72 characters in length. This includes white spaces.

3 ____ Misaligned Amino   The numbering under each 5th amino acid is misaligned. Do not use tab codes between numbers;
     Numbering   use space characters, instead.

4 ____ Non-ASCII   The submitted file was not saved in ASCII(DOS) text, as required by the Sequence Rules. Please
     ensure your subsequent submission is saved in ASCII text.

5 ____ Variable Length   Sequence(s) ____ contain n's or Xaa's representing more than one residue. Per Sequence Rules,
     each n or Xaa can only represent a single residue. Please present the maximum number of each
     residue having variable length and indicate in the <220>-<223> section that some may be missing.

6 ____ PatentIn 2.0   A "bug" in PatentIn version 2.0 has caused the <220>-<223> section to be missing from amino acid
     "bug"   sequence(s) _____. Normally, PatentIn would automatically generate this section from the
     previously coded nucleic acid sequence. Please manually copy the relevant <220>-<223> section to
     the subsequent amino acid sequence. This applies to the mandatory <220>-<223> sections for
     Artificial or Unknown sequences.

7 ____ Skipped Sequences   Sequence(s) ____ missing. If intentional, please insert the following lines for each skipped sequence:
     (OLD RULES)   (2) INFORMATION FOR SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
     (i)   SEQUENCE CHARACTERISTICS: (Do not insert any subheadings under this heading)
     (xi) SEQUENCE DESCRIPTION:SEQ ID NO:X: (insert SEQ ID NO where "X" is shown)
     This sequence is intentionally skipped

     Please also adjust the "(ii) NUMBER OF SEQUENCES:" response to include the skipped sequences.

8 ____ Skipped Sequences   Sequence(s) ____ missing. If intentional, please insert the following lines for each skipped sequence.
     (NEW RULES)   <210> sequence id number
     <400> sequence id number
     000

9 _✓_ Use of n's or Xaa's   Use of n's and/or Xaa's have been detected in the Sequence Listing.
     (NEW RULES)   Per 1.823 of Sequence Rules, use of <220>-<223> is MANDATORY if n's or Xaa's are present.
     In <220> to <223> section, please explain location of n or Xaa, and which residue n or Xaa represents.

10 ____ Invalid <213>   Per 1.823 of Sequence Rules, the only valid <213> responses are: Unknown, Artificial Sequence, or
     Response   scientific name (Genus/species). <220>-<223> section is required when <213> response is Unknown or
     is Artificial Sequence

11 ____ Use of <220>   Sequence(s) _____ missing the <220> "Feature" and associated numeric identifiers and responses.
     Use of <220> to <223> is MANDATORY if <213> "Organism" response is "Artificial Sequence" or
     "Unknown." Please explain source of genetic material in <220> to <223> section.
     (See "Federal Register," 06/01/1998, Vol. 63, No. 104, pp. 29631-32) (Sec. 1.823 of Sequence Rules)

12 ____ PatentIn 2.0   Please do not use "Copy to Disk" function of PatentIn version 2.0. This causes a corrupted file,
     "bug"   resulting in missing mandatory numeric identifiers and responses (as indicated on raw sequence
     listing). Instead, please use "File Manager" or any other manual means to copy file to floppy disk.

RECEIVED

SEP 0 7 2001

TECH CENTER 1600/2900

Page 1 of 6

#10
[handwritten]
1-9-10
1646

[stamp: OIPE JC11 SEP 0 4 2001 PATENT & TRADEMARK OFFICE]

RAW SEQUENCE LISTING
PATENT APPLICATION: US/09/489,198

DATE: 06/14/2001
TIME: 10:13:12

Input Set : A:\Sequence.txt
Output Set: N:\CRF3\06142001\I489198.raw

[handwritten: Does Not Comply — Corrected Diskette Needed — See pp. 1, 2, 5]

```
      3  <110> APPLICANT: CHUGAI SEIYAKU KABUSHIKI KAISHA.
      5  <120> TITLE OF INVENTION: Gene screening method using nuclear receptor
      7  <130> FILE REFERENCE: C1-901PCT
C-->  9  <140> CURRENT APPLICATION NUMBER: US/09/489,198
C--> 10  <141> CURRENT FILING DATE: 2000-01-20
     12  <150> PRIOR APPLICATION NUMBER: JP 09/212624
W--> 13  <151> PRIOR FILING DATE: (1997-7-22)   -> 1997-07-22
     15  <160> NUMBER OF SEQ ID NOS: 4
     17  <170> SOFTWARE: PatentIn Ver. 2.0
```

ERRORED SEQUENCES

[handwritten: Valid <212> responses: — DNA — RNA — PRT]

```
     19  <210> SEQ ID NO: 1
     20  <211> LENGTH: 507
E--> 21  <212> TYPE: (RPT)
     22  <213> ORGANISM: Mus musculus
     24  <400> SEQUENCE: 1
     25                                     Met Thr Gln Ala Val Lys Leu Ala
     26                                     1               5
     27  Ser Arg Val Phe His Arg Ile His Leu Pro Leu Gln Leu Asp Ala Ser
     28      10                  15                  20
     29  Leu Gly Ser Arg Gly Ser Glu Ser Val Leu Arg Ser Leu Ser Asp Ile
     30  25                  30                  35                  40
     31  Pro Gly Pro Ser Thr Leu Ser Phe Leu Ala Glu Leu Phe Cys Lys Gly
     32                  45                  50                  55
     33  Gly Leu Ser Arg Leu His Glu Leu Gln Val His Gly Ala Ala Arg Tyr
     34                  60                  65                  70
     35  Gly Pro Ile Trp Ser Gly Ser Phe Gly Thr Leu Arg Thr Val Tyr Val
     36              75                  80                  85
     37  Ala Asp Pro Thr Leu Val Glu Gln Leu Leu Arg Gln Glu Ser His Cys
     38      90                  95                  100
     39  Pro Glu Arg Cys Ser Phe Ser Ser Trp Ala Glu His Arg Arg Arg His
     40  105                 110                 115                 120
     41  Gln Arg Ala Cys Gly Leu Leu Thr Ala Asp Gly Glu Glu Trp Gln Arg
     42                  125                 130                 135
     43  Leu Arg Ser Leu Leu Ala Pro Leu Leu Leu Arg Pro Gln Ala Ala Ala
     44                  140                 145                 150
     45  Gly Tyr Ala Gly Thr Leu Asp Asn Val Val Arg Asp Leu Val Arg Arg
     46              155                 160                 165
     47  Leu Arg Arg Gln Arg Gly Arg Gly Ser Gly Leu Pro Gly Leu Val Leu
     48      170                 175                 180
     49  Asp Val Ala Gly Glu Phe Tyr Lys Phe Gly Leu Glu Ser Ile Gly Ala
     50  185                 190                 195                 200
     51  Val Leu Leu Gly Ser Arg Leu Gly Cys Leu Glu Ala Glu Val Pro Pro
     52                  205                 210                 215
     53  Asp Thr Glu Thr Phe Ile His Ala Val Gly Ser Val Phe Val Ser Thr
```

RAW SEQUENCE LISTING   DATE: 06/14/2001
PATENT APPLICATION: US/09/489,198   TIME: 10:13:12

--Input Set : A:\Sequence.txt
  Output Set: N:\CRF3\06142001\I489198.raw

```
54              220               225               230
55 Leu Leu Thr Met Ala Met Pro Asn Trp Leu His His Leu Ile Pro Gly
56         235               240               245
57 Pro Trp Ala Arg Leu Cys Arg Asp Trp Asp Gln Met Phe Ala Phe Ala
58     250               255               260
59 Gln Arg His Val Glu Leu Arg Glu Gly Glu Ala Ala Met Arg Asn Gln
60 265               270               275               280
61 Gly Lys Pro Glu Glu Asp Met Pro Ser Gly His His Leu Thr His Phe
62             285               290               295
63 Leu Phe Arg Glu Lys Val Ser Val Gln Ser Ile Val Gly Asn Val Thr
64         300               305               310
65 Glu Leu Leu Leu Ala Gly Val Asp Thr Val Ser Asn Thr Leu Ser Trp
66         315               320               325
67 Thr Leu Tyr Glu Leu Ser Arg His Pro Asp Val Gln Thr Ala Leu His
68     330               335               340
69 Ser Glu Ile Thr Ala Gly Thr Arg Gly Ser Cys Ala His Pro His Gly
70 345               350               355               360
71 Thr Ala Leu Ser Gln Leu Pro Leu Leu Lys Ala Val Ile Lys Glu Val
72             365               370               375
73 Leu Arg Leu Tyr Pro Val Val Pro Gly Asn Ser Arg Val Pro Asp Arg
74         380               385               390
75 Asp Ile Arg Val Gly Asn Tyr Val Ile Pro Gln Asp Thr Leu Val Ser
76         395               400               405
77 Leu Cys His Tyr Ala Thr Ser Arg Asp Pro Thr Gln Phe Pro Asp Pro
78     410               415               420
79 Asn Ser Phe Asn Pro Ala Arg Trp Leu Gly Glu Gly Pro Thr Pro His
80 425               430               435               440
81 Pro Phe Ala Ser Leu Pro Phe Gly Phe Gly Lys Arg Ser Cys Ile Gly
82             445               450               455
83 Arg Arg Leu Ala Glu Leu Glu Leu Gln Met Ala Leu Ser Gln Ile Leu
84         460               465               470
85 Thr His Phe Glu Val Leu Pro Glu Pro Gly Ala Leu Pro Ile Lys Pro
86         475               480               485
87 Met Thr Arg Thr Val Leu Val Pro Glu Arg Ser Ile Asn Leu Gln Phe
88     490               495               500
89 Val Asp Arg
90 505
92 <210> SEQ ID NO: 2
93 <211> LENGTH: 508
94 <212> TYPE: RPT
95 <213> ORGANISM: Homo sapiens
97 <400> SEQUENCE: 2
98 Met Thr Gln Thr Leu Lys Tyr Ala Ser Arg Val Phe His Arg Val Arg
99 1               5               10              15
100 Trp Ala Pro Glu Leu Gly Ala Ser Leu Gly Tyr Arg Glu Tyr His Ser
101             20              25              30
102 Ala Arg Arg Ser Leu Ala Asp Ile Pro Gly Pro Ser Thr Pro Ser Phe
103         35              40              45
104 Leu Ala Glu Leu Phe Cys Lys Gly Gly Leu Ser Arg Leu His Glu Leu
```

E--> (handwritten annotation pointing to line 94)

(handwritten) Valid responses:
- DNA
- RNA
- PRT

RAW SEQUENCE LISTING   DATE: 06/14/2001
PATENT APPLICATION: US/09/489,198   TIME: 10:13:12

Input Set : A:\Sequence.txt
Output Set: N:\CRF3\06142001\I489198.raw

```
105      50                      55                      60
106 Gln Val Gln Gly Ala Ala His Phe Gly Pro Val Trp Leu Ala Ser Phe
107 65                      70                      75                      80
108 Gly Thr Val Arg Thr Val Tyr Val Ala Ala Pro Ala Leu Val Glu Glu
109                      85                      90                      95
110 Leu Leu Arg Gln Glu Gly Pro Arg Pro Glu Arg Cys Ser Phe Ser Pro
111                      100                     105                     110
112 Trp Thr Glu His Arg Arg Cys Arg Gln Arg Ala Cys Gly Leu Leu Thr
113              115                     120                     125
114 Ala Glu Gly Glu Glu Trp Gln Arg Leu Arg Ser Leu Leu Ala Pro Leu
115      130                     135                     140
116 Leu Leu Arg Pro Gln Ala Ala Ala Arg Tyr Ala Gly Thr Leu Asn Asn
117 145                     150                     155                     160
118 Val Val Cys Asp Leu Val Arg Arg Leu Arg Arg Gln Arg Gly Arg Gly
119                      165                     170                     175
120 Thr Gly Pro Pro Ala Leu Val Arg Asp Val Ala Gly Glu Phe Tyr Lys
121              180                     185                     190
122 Phe Gly Leu Glu Gly Ile Ala Ala Val Leu Leu Gly Ser Arg Leu Gly
123              195                     200                     205
124 Cys Leu Glu Ala Gln Val Pro Pro Asp Thr Glu Thr Phe Ile Arg Ala
125      210                     215                     220
126 Val Gly Ser Val Phe Val Ser Thr Leu Leu Thr Met Ala Met Pro His
127 225                     230                      235                    240
128 Trp Leu Arg His Leu Val Pro Gly Pro Trp Gly Arg Leu Cys Arg Asp
129              245                     250                     255
130 Trp Asp Gln Met Phe Ala Phe Ala Gln Arg His Val Glu Arg Arg Glu
131              260                     265                     270
132 Ala Glu Ala Ala Met Arg Asn Gly Gly Gln Pro Glu Lys Asp Leu Glu
133              275                     280                     285
134 Ser Gly Ala His Leu Thr His Phe Leu Phe Arg Glu Glu Leu Pro Ala
135      290                     295                     300
136 Gln Ser Ile Leu Gly Asn Val Thr Glu Leu Leu Leu Ala Gly Val Asp
137 305                     310                     315                     320
138 Thr Val Ser Asn Thr Leu Ser Trp Ala Leu Tyr Glu Leu Ser Arg His
139              325                     330                     335
140 Pro Glu Val Gln Thr Ala Leu His Ser Glu Ile Thr Ala Ala Leu Ser
141              340                     345                     350
142 Pro Gly Ser Ser Ala Tyr Pro Ser Ala Thr Val Leu Ser Gln Leu Pro
143      355                     360                     365
144 Leu Leu Lys Ala Val Val Lys Glu Val Leu Arg Leu Tyr Pro Val Val
145      370                     375                     380
146 Pro Gly Asn Ser Arg Val Pro Asp Lys Asp Ile His Val Gly Asp Tyr
147 385                     390                     395                     400
148 Ile Ile Pro Lys Asn Thr Leu Val Thr Leu Cys His Tyr Ala Thr Ser
149              405                     410                     415
150 Arg Asp Pro Ala Gln Phe Pro Glu Pro Asn Ser Phe Arg Pro Ala Arg
151              420                     425                     430
152 Trp Leu Gly Glu Gly Pro Thr Pro His Pro Phe Ala Ser Leu Pro Phe
153              435                     440                     445
```

RAW SEQUENCE LISTING   DATE: 06/14/2001
PATENT APPLICATION: US/09/489,198   TIME: 10:13:12

Input Set : A:\Sequence.txt
Output Set: N:\CRF3\0614200\\I489198.raw

```
154 Gly Phe Gly Lys Arg Ser Cys Met Gly Arg Arg Leu Ala Glu Leu Glu
155     450             455             460
156 Leu Gln Met Ala Leu Ala Gln Ile Leu Thr His Phe Glu Val Gln Pro
157 465             470             475             480
158 Glu Pro Gly Ala Ala Pro Val Arg Pro Lys Thr Arg Thr Val Leu Val
159 ·               485             490             495
160 Pro Glu Arg Ser Ile Asn Leu Gln Phe Leu Asp Arg
161             500             505
```

<210> 4
<211> 2362
<212> DNA
<213> Homo sapiens

<220>
<221> CDS
<222> (1)...(1524)

Seq. #4

There is an "n" at position 1926 in sequence # 4. It is mandatory to have <220> to <223> features to explain what the "n" represents. See # 9 on the Error Summary Sheet.

VERIFICATION SUMMARY   DATE: 06/14/2001
PATENT APPLICATION: US/09/489,198   TIME: 10:13:13

        Input Set : A:\Sequence.txt
        Output Set: N:\CRF3\06142001\I489198.raw

L:9 M:270 C: Current Application Number differs, Replaced Application Number
L:10 M:271 C: Current Filing Date differs, Replaced Current Filing Date
L:13 M:256 W: Invalid Numeric Header Field, Wrong Prior FILING DATE:YYYY-MM-DD
L:21 M:310 E: (3) Wrong or Missing Sequence Type, TYPE:
L:94 M:310 E: (3) Wrong or Missing Sequence Type, TYPE:
L:399 M:258 W: Mandatory Feature missing, <223> not found for SEQ ID#:4
L:399 M:341 W: (46) "n" or "Xaa" used, for SEQ ID#:4